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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE, MARTENS, OLSON & BEAR, LLP			ROMEO, DAVID S	
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1647

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,514	EATON ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 July 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-7,9 and 11-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-7,9 and 11-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>0705</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 07/01/2005 has been entered.

Claims 4-7, 9, 11-17 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:***Claim Rejections - 35 USC §§ 101, 112***

Claims 4-7, 9, 11-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants' discussion of the utility legal standard is acknowledged. However, the present rejection is based upon Applicants' failure to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. In addition, The M.P.E.P. reminds Office personnel that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. The countervailing evidence shows that the significance or relevance of PRO874 mRNA expression to the asserted therapeutic and diagnostic utilities of the claimed PRO874 polypeptide is unknown, and that the

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skilled artisan would have a reasonable, legitimate basis to doubt the utility of the PRO874 polypeptide. In addition, none of the arguments, exhibits, declarations, or other evidence provided by applicants provides any data concerning the expression of the claimed polypeptides in normal lung, lung tumor, or any other type of tissue sample. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility.

The examiner disagrees with Applicants' characterization of the utility guidance provided by M.P.E.P. § 2107.01 III because unlike the situation wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, in the present situation Applicants' have not provided any testing of the expression, role, or activity of the PRO874 polypeptide. Regarding the requirement for further experimentation as a basis for lack of utility, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities (M.P.E.P. § 2107.01 I). In the present case, the evidence shows that the asserted diagnostic or therapeutic utilities of the PRO874 gene and polypeptide require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use.

The examiner also disagrees with Applicants reliance on "[t]o violate [35 U.S.C.] 101 the claimed device must be totally incapable of achieving a useful result" because the evidence that PRO874 mRNA is more highly expressed in normal lung as compared to lung tumor is insufficient evidence that the claimed PRO874 polypeptide will function as a cancer diagnostic or therapeutic. Applicants have failed to establish the correlation between PRO874 mRNA expression and PRO874 polypeptide expression in normal lung, lung tumor, or any other type of

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tissue sample. It cannot be determined if the difference, if any, in PRO874 mRNA expression between normal lung and lung tumor is significant or insignificant, relevant or irrelevant, disease-dependent or disease-independent. Therefore, the probability that the asserted utilities are true is not ascertainable and there is no reason for the skilled artisan to believe that it is more likely than not that the claimed PRO874 polypeptide could be used as a cancer diagnostic or therapeutic.

As noted by applicants, an Applicants' assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." The evidence provides a reason for one skilled in the art to question the objective truth of the statement of diagnostic or therapeutic use of the PRO874 polypeptide. In the absence of any information on the role, activity, or expression of the PRO874 polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer.

Unlike situations wherein specific uses are supported by test data, in the present case Applicants have not provided any testing of the role, expression, or activity of the PRO874 polypeptide in any type of tissue. The examiner is not arguing that there is no correlation between gene expression and protein expression. The examiner is not arguing that the techniques that measure gene levels, such as microarray analysis, differential display, and quantitative PCR, are without merit. The examiner is arguing that Applicants have failed to disclose or establish the correlation between PRO874 mRNA expression and PRO874

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polypeptide expression in normal lung, lung tumor, or any other type of tissue sample.

Therefore, the probability that the asserted utilities are true is not ascertainable. Even if the present results provided reliable evidence that PRO874 mRNA is expressed at least two-fold higher in normal lung as compared to lung tumor the skilled artisan still would not know if this

5 difference is disease-dependent or disease-independent. Even if the examiner were to assume that the present results with PRO874 mRNA expression could reasonably be correlated with PRO874 polypeptide expression, it still could not be ascertained if the assumed difference in PRO874 polypeptide expression would be disease-dependent or disease-independent because the skilled artisan would not know if the difference in PRO874 mRNA expression is disease-

10 dependent or disease-independent. The specification lacks a "sufficient correlation" between the test performed on PRO874 mRNA expression and the asserted utility of the claimed PRO874 polypeptide. Because Applicants have failed to establish any correlation between PRO874 mRNA expression and PRO874 polypeptide expression in normal lung, lung tumor, or any other type of tissue sample, Applicants have failed to establish a significant probability that PRO874
15 polypeptide is useful as a cancer diagnostic or therapeutic. There is no reason for the skilled artisan to believe that it is more likely than not that the claimed PRO874 polypeptide could be used as a cancer diagnostic or therapeutic. The skilled artisan would not know if or how expression of the claimed polypeptides would change in tumors.

Applicants argue that they have established that the gene encoding the PRO874
20 polypeptide is differentially expressed in certain cancers compared to normal tissue and is useful as a diagnostic tool, and therefore the corresponding polypeptide and antibodies are useful as diagnostic tools, as evidenced by the Grimaldi declaration filed 12/10/2004 (Exhibit 1).

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Applicants' arguments have been fully considered but they are not persuasive. The assertions (Grimaldi declaration filed 12/10/2004, Exhibit 1) that "Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual" (paragraph 5), "it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA" (paragraph 6), "The precise levels of gene expression are irrelevant" (paragraph 7), and "If a difference is detected, ... the gene and its corresponding polypeptide ... are useful for diagnostic purposes" (paragraph 7) are conclusory and unsupported. Furthermore, the declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in lung tumor, normal lung, or any other type of tissue sample. The specification does not provide any evidence that indicates if the results were statistically significant. The specification does not teach the level of reproducibility or reliability of the results seen in Example 18. There are no absolute levels of PRO874 mRNA in control or tumor tissue disclosed. The likelihood that the level of PRO874 from a lung tissue sample from a patient with lung cancer would be higher or lower when compared with normal tissue is unknown. It is unknown how many samples would be needed or what sensitivity would be needed. It is unknown if the normal tissue would have to be a pooled sample or from a single individual. Applicants only teach that PRO874 mRNA was "more highly expressed in" normal lung as compared to lung tumor, and this does not enable the skilled artisan to differentiate between expression levels in order to diagnose any diseases. Furthermore, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu (J Proteome Res. 2003 Jul-Aug;2(4):405-12, cited by Applicants) analyzed 2286 genes that showed

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a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (page 408, middle of right column). Hu discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among
5 genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Hu also provides evidence that the skilled artisan recognizes that in differential analysis of mRNA expression there are biologically relevant results as well as biologically irrelevant results.

See Hu, which teaches:

10 “[h]igh-throughput technologies, such as proteomic screening and DNA micro-arrays, produce vast amounts of data requiring comprehensive analytical methods to decipher the biologically relevant results” (Abstract).

15 “In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study” (page 405, left column, full paragraph 1).

20 “It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful. ... For genes displaying a 5-fold change or less ... there was no evidence of a correlation between altered gene expression and a known role in the disease. This reflects ... genes whose modest changes in expression may be unrelated to the disease.” Paragraph bridging pages 411-412.

25 Therefore, in any microarray experiment further research is required in order to determine which results are biologically relevant.

Furthermore, Labaer (Nat Biotechnol. 2003 Sep;21(9):976-7) teaches:

30 In the accelerating quest for disease biomarkers, the use of high-throughput technologies, such as DNA microarrays and proteomics experiments, has produced vast datasets identifying thousands of genes whose expression patterns differ in diseased versus normal samples. Although many of these differences

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may reach statistical significance, they are not always biologically meaningful. For example, reports of mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between the samples. Page 976, paragraph bridging middle and right columns.

In addition, Wang (Trends Pharmacol Sci. 1996 Aug;17(8):276-9, cited by Applicants) indicates that differential display is the first of many steps required in the discovery of a novel pharmacological target, especially given that the function of the factor is most likely unknown.

Therefore, further action should be taken to characterize the functions of a particular gene of interest, including ... validation for the importance of the gene in disease processes. See page 279, column 2, full paragraph 1.

Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form readily usable by the skilled artisan and significant further experimentation is necessary. It cannot be determined if the difference, if any, of PRO874 mRNA expression between normal lung and lung tumor is significant or insignificant, disease-dependent or disease-independent, relevant or irrelevant.

The skilled artisan would not know if the difference in PRO874 mRNA expression is significant or insignificant, relevant or irrelevant, disease-dependent or disease-independent. Hence, the significance or relevance of PRO874 mRNA expression to lung tumor cannot be ascertained.

Moreover, the present specification does not provide any data regarding the level of expression, activity, or role in cancer of the PRO874 polypeptide. Hence, the specification fails to establish the correlation between PRO874 mRNA expression and PRO874 polypeptide expression in normal lung, lung tumor, or any other type of tissue sample. Even if one were to assume that the present results with PRO874 mRNA expression could reasonably be correlated with PRO874

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polypeptide expression, it still could not be ascertained if the assumed difference in PRO874 polypeptide expression is disease-dependent or disease-independent because one would not know if the difference in PRO874 mRNA expression is significant or insignificant, relevant or irrelevant, disease-dependent or disease-independent. Therefore, the probability that the asserted utilities for the claimed PRO874 polypeptide are true is not ascertainable. There is no reason for the skilled artisan to believe that it is more likely than not that the claimed PRO874 polypeptide could be used as a cancer diagnostic or therapeutic.

Furthermore, even in cases where genes are differentially expressed in a cancer and overexpression of the corresponding protein products in the cancer is verified, the art indicates that further experimentation is necessary to establish the usefulness of these genes and gene products for diagnosis, prognosis, and treatment of cancer. For example, Yousef (Cancer Res. 2003 May 1;63(9):2223-7) indicates that many members of the human kallikrein (KLK) gene family are differentially regulated in ovarian cancer and have potential as diagnostic and/or prognostic markers. Yousef performed *in silico* analyses of the expression pattern of the 15 human KLK genes in normal and cancerous ovarian tissues and cell lines. Yousef found that seven KLK genes (KLK5, KLK6, KLK7, KLK8, KLK10, KLK11, and KLK14) are up-regulated in ovarian cancer. Yousef experimentally verified the overexpression of six KLK proteins in cancer versus normal or benign tissues with highly sensitive and specific immunofluorometric assays. A statistically significant stepwise increase in protein levels was found among normal, benign, and cancerous ovarian tissues. The expression of five KLKs showed a strong degree of correlation at the protein level, suggesting the existence of a common mechanism or pathway that controls the expression of this group of adjacent genes during ovarian cancer progression.

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See the Abstract. However, Yousef indicates that further experimentation is necessary to establish the usefulness of these KLKs for diagnosis, prognosis, and treatment of ovarian cancer (page 2226, right column, last paragraph). Therefore, Yousef, which discloses more about a potential cancer diagnostic, prognostic, or treatment than the present specification discloses about PRO874, is consistent with and supports the examiner's position that the present specification fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention, and that the present disclosure is simply a starting point for further research and investigation into potential practical uses of the claimed invention. Hence, in the present case the characterization of PRO874 mRNA as being "more highly expressed in" normal lung as compared to lung tumor does not provide an immediate benefit to the public for the claimed PRO874 polypeptide.

Applicants argue that the Office has mischaracterized Applicants' asserted utility for the claimed polypeptides. Applicants' arguments have been fully considered but they are not persuasive. The Grimaldi declaration filed 12/10/2004 (Exhibit 2) asserts that:

"Comparison of gene expression levels in normal versus diseased tissue has important implications both diagnostically and therapeutically." Paragraph 6.

"... identification of both gene expression and protein expression enables more accurate tumor classification ..." Paragraph 7.

The Ashkenazi declaration filed 12/10/2004 (Exhibit 6) asserts that:

the "absence of gene product overexpression still provides significant information for cancer diagnosis and treatment." Paragraph 6.

Applicants are arguing that whatever the expression level and whatever the correlation, the claimed polypeptides are useful because skilled artisans could figure out for themselves what

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any observed experimental result might mean. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form" because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent, or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect or characterize the tumor. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility.

It is clear that Applicants seek a per se rule, that any detectable difference in mRNA expression is significant, relevant, and tumor-dependent and that any such difference would require a per se rule of utility for the encoded polypeptide. This standard, however, is not what the art teaches. The skilled artisan would not know if or how PRO874 polypeptide expression would change in normal lung and lung tumor.

Applicants argue that they have established that the accepted understanding in the art is that there is a reasonable correlation between the level of mRNA and the level of the encoded protein. Applicants argue that a necessary correlation is not required to establish an asserted utility, because there only need be a reasonable correlation. Applicants argue that the declarations of Grimaldi (Exhibit 2, filed 12/10/2004) and Polakis (Exhibit 3, filed 12/10/2004), as supported by Molecular Biology of the Cell, 3rd ed. (Exhibit 1, filed 07/01/2005), Molecular Biology of the Cell, 4th ed. (Exhibits 4 and 2, filed 12/10/2004 and 07/01/2005, respectively), as further supported by Lewin (Exhibit 3, filed 07/01/2005), and as additionally supported by Zhigang (Exhibit 4, filed 07/01/2005) and Meric (Exhibit 5, filed 07/01/2005), establish that

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there is a positive correlation between changes in mRNA levels and changes in the corresponding protein levels. Applicants' arguments have been fully considered but they are not persuasive. There must be a necessary correlation between PRO874 mRNA expression and PRO874 polypeptide expression in order for the claimed PRO874 polypeptide to function as the asserted cancer diagnostic or therapeutic. Applicants anticipate that for the PRO874 gene the analysis of transcript levels are indicative of the levels of PRO874 protein expression (Example 18, page 140, paragraph 00530). Unlike Allman (Blood. 1996 Jun 15;87(12):5257-68), Applicants have not provided any testing of the role, activity, or expression of the PRO874 polypeptide. Allman is evidence that the skilled artisan would not know if or how PRO874 polypeptide levels would change in tumors. To argue that Allman supports applicants' position because Allman did not obtain the anticipated results is akin to arguing that the skilled artisan could experiment with PRO874 mRNA and polypeptide levels and determine for themselves what any observed experimental result might mean.

Applicants assume that the changes in PRO874 transcript levels are indicative of changes in PRO874 polypeptide levels. However, Haynes (Electrophoresis. 1998 Aug;19(11):1862-71, cited by Applicants) states:

"Interpretation of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are indicative of the levels of protein expression" (page 1863, left column, full paragraph 1),

Haynes goes on to state:

"These results suggest that even for a population of genes predicted to be relatively homogenous ..., the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (page 1863, left column, full paragraph 1).

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Haynes concludes that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript. Haynes provides evidence that protein expression levels are not predictable from the mRNA expression levels. Haynes cites this lack of predictability as one of the main reasons for proteome analysis to become an essential component in the comprehensive analysis of biological systems. Paragraph bridging pages 1862-1863; page 1863, left column, full paragraph 1. Haynes further teaches:

“it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis” page 1863, right column, full paragraph 2).

In view of the fact that protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript and the fact that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, the skilled artisan would not know if the disclosed change in PRO874 mRNA expression is associated with a corresponding change in the level of PRO874 protein.

Regarding the correlation of mRNA and protein expression levels, Gygi (Mol Cell Biol. 1999 Mar;19(3):1720-30, cited by Applicants) states:

The correlation between mRNA and protein levels of the genes selected as described above is shown in Fig. 5. For the entire group (106 genes) for which a complete data set was generated, there was a general trend of increased protein levels resulting from increased mRNA levels. The Pearson product moment correlation coefficient for the whole data set (106 genes) was 0.935. This number is highly biased by a small number of genes with very large protein and message levels. A more representative subset of the data is shown in the inset of Fig. 5. It shows genes for which the message level was below 10 copies/cell and includes 69% (73 of 106 genes) of the data used in the study. The Pearson product moment correlation coefficient for this data set was only 0.356. We also found that levels of protein expression coded for by mRNA with comparable abundance varied by as much as 30-fold and that the mRNA levels coding for proteins with comparable expression levels varied by as much as 20-fold. Page 1726, left column, full paragraph 1.

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Gygi goes on to state:

We therefore expect that the correlation for all yeast proteins or for a random selection would be less than 0.4. The observed level of correlation between mRNA and protein expression levels suggests the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translational control and control of protein half-life. Since these mechanisms are also active in higher eukaryotic cells, we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells. Page 1727, paragraph bridging left and right columns.

Gygi concludes:

... this study examined the relationship between yeast protein and message levels and revealed that transcript levels provide little predictive value with respect to the extent of protein expression. Page 1730, left column.

Haynes and Gygi teach that protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript and that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis. Hence, the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer. Furthermore, the present specification only presents data showing a relative difference in PRO874 mRNA levels. There is no evidence that PRO874 mRNA was highly expressed. Applicants have not provided any comparison of the levels of PRO874 polypeptide expression. Furthermore, the significance or relevance of PRO874 mRNA expression to lung tumor cannot be ascertained because the skilled artisan would not know if the difference in PRO874 mRNA expression is significant or insignificant, relevant or irrelevant, disease-dependent or disease-independent, as supported by Hu and LaBaer. Even if one were to assume that the present results with PRO874 mRNA expression could reasonably be correlated with PRO874 polypeptide expression, it still could not be ascertained if the assumed difference

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in PRO874 polypeptide expression is disease-dependent or disease-independent because one would not know if the difference in PRO874 mRNA expression is significant or insignificant, relevant or irrelevant, disease-dependent or disease-independent.

The Grimaldi declaration has been considered. However, in the present case it is
5 unknown if the reported differences in PRO874 mRNA expression are tumor-dependent or tumor-independent. It is acknowledged that there are examples in the art where mRNA expression and protein expression correlate. However, there are examples where they do not correlate, as evidenced by Allman. Unlike Allman, Applicants have not provided any testing of the role, activity, or expression of the PRO874 polypeptide. Furthermore, the declaration does
10 not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in lung tumor, normal lung, or any other type of tissue sample.

The Polakis declaration has been considered. However, given the evidence in the art that increased mRNA levels do not necessarily correlate with increased protein levels and the paucity of information given regarding the expression of PRO874 mRNA in tumors, one skilled in the art
15 would not know if PRO874 mRNA expression was disease-dependent or disease-independent, would not know if or how PRO874 polypeptide expression would change in tumors and would have a reasonable, legitimate basis to doubt the utility of the PRO874 polypeptide. Furthermore, the declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in lung tumor, normal lung, or any
20 other type of tissue sample.

Applicant argues that the examiner must accept an opinion from a qualified expert. This has been fully considered but is not found to be persuasive. In the instant case, the nature of the

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fact is whether or not there is a correlation between PRO874 mRNA levels and PRO874 protein levels. However, the present specification does not teach the level of reproducibility or the level of reliability of the results seen in Example 18. The skilled artisan would not know if these differences were disease-dependent or disease-independent. Applicants have not provided any testing of the expression, role, or activity of the PRO874 polypeptide. Even if the examiner were to assume that the present results with PRO874 mRNA expression could reasonably be correlated with PRO874 polypeptide expression, it still could not be ascertained if the assumed differences in PRO874 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the PRO874 mRNA differences would be disease-dependent or disease-independent. While Dr. Polakis refers to his experiments, only conclusions were set forth in the declaration. No data or results were presented for independent analysis. Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to Dr. Polakis.

Molecular Biology of the Cell, 3rd ed. (Exhibit 1, filed 07/01/2005) and 4th ed. (Exhibits 4 and 2, filed 12/10/2004 and 07/01/2005, respectively), Lewin (Exhibit 3, filed 07/01/2005), Zhigang (Exhibit 4, filed 07/01/2005), and Meric (Exhibit 5, filed 07/01/2005) are acknowledged. However, Molecular Biology of the Cell (Exhibit 1, filed 07/01/2005) acknowledges that "other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made" (page 453, last full paragraph). Molecular Biology of the Cell, 4th ed. (Exhibits 4 and 2, filed 12/10/2004 and 07/01/2005, respectively) acknowledges

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that the final level of protein depends upon the efficiency with which each of the many steps from DNA to protein is performed (page 363, last full paragraph and page 364, Figure 6-90).

Lewin (Exhibit 3, filed 07/01/2005) acknowledges that “production of RNA cannot inevitably be equated with production of protein” (paragraph bridging pages 847-848). Molecular Biology of

5 the Cell and Lewin support and are consistent with the examiner’s position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The examiner does not agree that Figure 6-3 (Exhibit 2, page 202) illustrates a basic
10 principle that there is a correlation between increased gene expression and increased protein expression. This figure only illustrates that different genes can be expressed with different efficiencies. Applicants have failed to explain the nexus between what this figure actually illustrates and what Applicants purport this figure to illustrate.

It is acknowledged that Zhigang presents data showing a high degree of correlation
15 between PSCA protein and mRNA expression (page 4 of 7, right column, last sentence).

However, exceptions were noted (paragraph bridging pages 3 of 7 and 4 of 7; page 4 of 7, left column, full paragraph 1). Thus, Zhigang supports and is consistent with the examiner’s position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about
20 the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention.

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It is acknowledged that Meric states that the “fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells” (page 971, right column, first paragraph of “Introduction”). However, the present specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO874 polypeptide. Therefore, the difference in PRO874 polypeptide expression between cancer cells and normal cells is unknown, and thus not exploitable. Meric also acknowledges that several alterations in translational control occur in cancer (page 971, Abstract) and that gene expression is quite complicated (page 971, right column, first paragraph of “Introduction”), suggesting that protein levels can be modulated independently of the level of mRNA. Thus, Meric supports and is consistent with the examiner’s position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer and that the present application fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention.

The examiner is not arguing that the techniques that measure gene levels, such as microarray analysis, differential display, and quantitative PCR, are without merit. The examiner is arguing that Applicants have failed to establish the correlation between PRO874 mRNA expression and PRO874 polypeptide expression in normal lung, lung tumor, or any other type of tissue sample. Therefore, the probability that the asserted utilities are true is not ascertainable. The skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer. There is no reason for the skilled artisan to believe that it is more likely than not that the claimed PRO874 polypeptide could be used as a cancer diagnostic or therapeutic.

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The examiner does not agree that the caveat in Example 12 of the utility guidelines is applicable to the present situation because unlike the situation wherein the specification discloses that receptor A is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells, in the present case Applicants rely on a qualitative comparison of PRO874 mRNA expression between tumor tissue and normal samples in order to establish utility for the presently claimed PRO874 polypeptide. However, the present specification does not teach the level of reproducibility or the level of reliability of the results seen in Example 18. The skilled artisan would not know if this difference is disease-dependent or disease-independent. Furthermore, Applicants have not provided any testing of the expression, role, or activity of the PRO874 polypeptide. Even if the examiner were to assume that the present results with PRO874 mRNA expression could reasonably be correlated with PRO874 polypeptide expression, it still could not be ascertained if the assumed difference in PRO874 polypeptide expression would be disease-dependent or disease-independent because the skilled artisan would not know if the difference in PRO874 mRNA expression is disease-dependent or disease-independent. The specification lacks a "sufficient correlation" between the test performed on PRO874 mRNA expression and the asserted utility of the claimed PRO874 polypeptide. Because Applicants have failed to establish any correlation between PRO874 mRNA expression and PRO874 polypeptide expression in normal lung, lung tumor, or any other type of tissue sample, Applicants have failed to establish a significant probability that PRO874 polypeptide is useful as a cancer diagnostic or therapeutic. There is no reason for the skilled artisan to believe that it is more likely than not that the claimed PRO874 polypeptide could be used as a cancer diagnostic or therapeutic.

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Exhibits 6-9 (filed 07/01/2005) are acknowledged. As Applicants recognize, each case must be decided on its own merits based on the evidence of record.

Applicants' conclusion regarding the utility of the claimed invention has been considered but it is not persuasive. In the present case, the differential analysis of PRO874 mRNA expression does not prove that the PRO874 polypeptide will perform as a cancer diagnostic or therapeutic. The differential expression of the PRO874 polynucleotide cannot be equated to and has not been adequately correlated with the contemplated cancer diagnostics or therapeutics of the claimed polypeptides. The PRO874 polypeptide has not been tested to the extent that utility would be known to those of skill in the art.

Claims 4-7, 9, 11-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue that they have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants' arguments have been fully considered but they are not persuasive. As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection

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properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C.

112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection

that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101

rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an

5 appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Claims 4, 5, 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply

with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with

10 which it is most nearly connected, to make and/or use the invention.

Applicants argue that the skilled artisan would know how to make and use the claimed polypeptides. Applicants' arguments have been fully considered but they are not persuasive.

The limitation "wherein said isolated polypeptide is encoded by ... tumor" is a limitation of the nucleic acid molecule encoding the claimed polypeptides. It is not a limitation of the

15 claimed polypeptides. As such, it does not limit the expression, function, or activity of the claimed polypeptides.

Regarding the limitation "wherein said isolated polypeptide is more highly expressed ... tumor," no information is provided in the differential analysis of PRO874 polynucleotide

expression regarding the level of expression, activity, or role in cancer of the PRO874

20 polypeptide. In the absence of this information a skilled practitioner would have to resort to a

substantial amount of undue experimentation in the form of characterization of the PRO874

polypeptide and validation of its association with lung tumors. It is this additional

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characterization of that single disclosed example of PRO874 mRNA expression that is required in order for the skilled artisan to obtain the information necessary to practice the full scope of the claimed invention that constitutes undue experimentation. To the extent that Applicants rely on a central dogma, a significant probability, or reasonable correlation as discussed in their reply to the utility rejection, these arguments have been fully considered but they are not persuasive for the same reasons that they were not persuasive in the rejection for lack of utility. Therefore, the limitation "wherein said isolated polypeptide is more highly expressed ... tissue" does not enable the claimed invention.

Claims 14-17 recite the limitation "wherein said polypeptide ... can be used to generate an antibody" These claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of their biological activity. To obtain a valid patent, a patent application must be filed that contains a full and clear disclosure of the invention in the manner prescribed by 35 U.S.C. 112, first paragraph. The requirement for an adequate disclosure ensures that the public receives something in return for the exclusionary rights that are granted to the inventor by a patent. If mere antigenic cross-reactivity were the test for enablement under § 112, Applicants could obtain patent rights that may confer power to block off whole areas of scientific development related to the biologic activity of the polypeptide, for which Applicants have not provided any disclosure. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO874 (SEQ ID NO: 10), which is ideally suited to the making of antibodies to itself, would enable any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biologic activities, when the specification provides no disclosure of any biological activity. Therefore, the scope of

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enablement provided to the skilled artisan by the disclosure is not commensurate with the scope of protection sought by the claims.

Claims 4, 5, 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that based on the level of skill in the art, the cloning of PRO874, the differential analysis of PRO874 expression, the actual reduction to practice of SEQ ID NO: 9 and SEQ ID NO: 10, and the functional limitations, the skilled artisan would know that Applicants were in possession of the claimed invention. Applicants' arguments have been fully considered but they are not persuasive.

The limitation "wherein said isolated polypeptide is encoded by ... tissue" is a limitation of the nucleic acid molecule encoding the claimed polypeptides. It is not a limitation of the claimed polypeptides. As such, it does not limit or describe the expression, function, or activity of the claimed polypeptides.

Regarding the limitation "wherein said isolated polypeptide is more highly expressed ... tissue", no information is provided in the differential analysis of PRO874 polynucleotide expression regarding the level of expression, activity, or role in cancer of the PRO874 polypeptide. The examiner has cited countervailing evidence to show that the skilled artisan would have a legitimate basis to doubt the utility of the PRO874 polypeptide because the skilled

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artisan recognizes that protein levels are not always consistent with mRNA levels. This evidence provides a reason for one skilled in the art to question the objective truth of the statement of diagnostic or therapeutic use of the claimed polypeptides. In the absence of any information on the role, activity, or expression of the PRO874 polypeptide in cancer, the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer. Therefore, the present disclosure does not reasonably convey to the skilled artisan that the present inventors had possession of the claimed invention. To the extent that Applicants rely on a central dogma, a significant probability, or reasonable correlation as discussed in the reply to the utility rejection in the last Office action, these arguments have been fully considered but they are not persuasive for the same reasons that they were not persuasive in the rejection for lack of utility and enablement.

Claims 14-17 recite the limitation "wherein said polypeptide ... can be used to generate an antibody" These claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of their biological activity. Applicants have not described the biologic activity of the PRO874 polypeptide or any of its variants. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO874, which is ideally suited to the making of antibodies to itself, would describe any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biologic activities, when the specification does not describe any biological activity. Therefore, the claimed subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Because the specification does not describe any

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biological activity of the claimed polypeptides and because the claims are not limited to any specific biologic activity of the claimed polypeptides, the present claims are not analogous to example 14 of the written description guidelines.

Regarding other U. S. Patents that may have issued containing claims to variant
5 polynucleotides and polypeptides (Exhibits 10-15), suffice it to say that each case must be decided on its own merits based on the evidence of record.

Claims 4-7, 9, 11-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which
10 was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that paragraph 0196 combined with Figure 10 conveys with reasonable clarity that Applicants were in possession of the claimed invention. Applicant's arguments have
15 been fully considered but they are not persuasive. Paragraph 0196 discloses that it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides. However, the species methionine residue #34 as the starting amino acid is not supported by this generic disclosure because there is no express, implicit, or inherent support
20 for this species to the exclusion of all the other species. In other words, the disclosure would not reasonably lead the skilled artisan to this particular species.

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Applicants argue that SEQ ID NO: 9 inherently discloses the polypeptides of SEQ ID NO: 10 starting at any of the eight methionine residues, and therefore, Applicants were clearly in possession "... nucleotides 100-966 of the cDNA ...". Applicant's arguments have been fully considered but they are not persuasive for the same reasons that the disclosure would not reasonably lead the skilled artisan to the species methionine residue #34 as the starting amino acid. There is no evidence of record that the naturally occurring PRO874 polypeptide actually starts at methionine residue #34.

Applicants argue that the examiner has misstated the test for compliance with the written description requirement. Applicant's arguments have been fully considered but they are not persuasive. The species methionine residue #34 as the starting amino acid is not supported by the generic disclosure because there is no express, implicit, or inherent support for this species to the exclusion of all the other species. Therefore, the specification does not convey with reasonable clarity that Applicants were in possession of the invention now claimed.

Applicants argue that Figure 10 implicitly discloses the 81-109 and 232-253 fragments of SEQ ID NO: 10 and that the examiner's argument is moot in light of the present claim amendments. Applicant's arguments have been fully considered but they are not persuasive. Figure 10 discloses that SEQ ID NO: 10 possesses several transmembrane domains. Thus, the intra- and extra-cellular domains depend on how the polypeptide is arranged in the membrane. Neither Figure 10 nor the specification disclose how the polypeptide is arranged in the membrane. Although the specification discloses a fragment of a PRO polypeptide that is the extracellular domain with or without the signal peptide, the specification does not disclose a fragment of a PRO polypeptide that is the intracellular domain. The newly added limitations

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"81-109" and "232-253" imply that "81-109" and "232-253" are the extracellular domains.

Support for the one arrangement implied by the present limitations cannot be found in the disclosure as originally filed. Hence, the newly added limitations constitute new matter.

Conclusion

No claims are allowable.

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DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
SEPTEMBER 2, 2005